This application also is a continuation-in-part of the following U.S. patent applications: Serial No. 09/302,158, filed April 29, 1999; and Serial No. 09/629,599, filed July 31, 2000, now U.S. Patent No. 6,469,311.

U.S. Patent Application Serial No. 09/302,158, in turn, is a divisional continuation application of U.S. Patent Application Serial No. 09/146,081, filed September 2, 1998, now U.S. Patent No. 6,187,267. The '081 application, in turn, is a continuation of the following patent applications: U.S. Patent Application Serial No. 09/062,472, filed April 17, 1998, now U.S. Patent No. 6,071,748; PCT Patent Application Serial No. PCT/US98/14575, filed July 15, 1998, now abandoned; U.S. Patent Application Serial No. 09/118,141, filed July 16, 1998, now U.S. Patent No. 6,313,960; U.S. Patent Application Serial No. 09/118,310, filed July 16, 1998, now U.S. Patent No. 6,033,100; U.S. Patent Application Serial No. 09/118,341, filed July 16, 1998, now U.S. Patent No. 6,025,985; U.S. Patent Application Serial No. 09/144,575, filed August 31, 1998, now U.S. Patent No. 6,159,425; and U.S. Patent Application Serial No. 09/144,578, filed August 31, 1998. These parent applications, in turn, claim priority from additional applications, as identified therein. The '081 application, in turn, also (directly and/or through its parent applications) is based upon and claims benefit under 35 U.S.C. § 119(e) of the following U.S. provisional patent applications, each of which is now abandoned: Serial No. 60/052,876, filed July 16, 1997; Serial No. 60/059,639, filed September 20, 1997; Serial No. 60/063,811, filed October 31, 1997; Serial No. 60/072,499, filed January 26, 1998; Serial No. 60/072,780, filed January 27, 1998; Serial No. 60/075,414, filed February 20, 1998; Serial No. 60/075,806, filed February 24, 1998;

Serial No. 60/082,253, filed April 17, 1998; Serial No. 60/084,167, filed May 4, 1998; Serial No. 60/085,335, filed May 13, 1998; Serial No. 60/085,500, filed May 14, 1998; Serial No. 60/089,848, filed June 19, 1998; Serial No. 60/094,275, filed July 27, 1998; Serial No. 60/094,276, filed July 27, 1998; and Serial No. 60/094,306, filed July 27, 1998.

U.S. Patent Application Serial No. 09/629,599, in turn, is a continuation of U.S. Patent Application Serial No. 09/160,533, filed September 24, 1998, now U.S. Patent No. 6,097,025. The '533 application, in turn, is a continuation of the following patent applications: U.S. Patent Application Serial No. 09/062,472, filed April 17, 1998, now U.S. Patent No. 6,071,748; PCT Patent Application Serial No. PCT/US98/14575, filed July 15, 1998, now abandoned; U.S. Patent Application Serial No. 09/118,141, filed July 16, 1998, now U.S. Patent No. 6,313,960; U.S. Patent Application Serial No. 09/118,310, filed July 16, 1998, now U.S. Patent No. 6,033,100; U.S. Patent Application Serial No. 09/118,341, filed July 16, 1998, now U.S. Patent No. 6,025,985; U.S. Patent Application Serial No. 09/144,575, filed August 31, 1998, now U.S. Patent No. 6,159,425; U.S. Patent Application Serial No. 09/144,578, filed August 31, 1998; U.S. Patent Application Serial No. 09/146,081, filed September 2, 1998, now U.S. Patent No. 6,187,267; U.S. Patent Application Serial No. 09/156,318, filed September 18, 1998, now U.S. Patent No. 6,258,326; and U.S. Patent Application Serial No. 09/478,819, filed January 5, 2000, now U.S. Patent No. 6,488,892. These parent applications, in turn, claim priority from additional applications, as identified therein. The '533 application, in turn, also (directly and/or through its parent applications) is based upon and claims benefit under 35 U.S.C.

§ 119(e) of the following U.S. provisional patent applications, each of which is now abandoned: Serial No. 60/063,811, filed October 31, 1997; Serial No. 60/072,499, filed January 26, 1998; Serial No. 60/072,780, filed January 27, 1998; Serial No. 60/075,414, filed February 20, 1998; Serial No. 60/075,806, filed February 24, 1998; Serial No. 60/082,253, filed April 17, 1998; Serial No. 60/084,167, filed May 4, 1998; Serial No. 60/085,335, filed May 13, 1998; Serial No. 60/085,500, filed May 14, 1998; Serial No. 60/089,848, filed June 19, 1998; Serial No. 60/094,275, filed July 27, 1998; Serial No. 60/094,276, filed July 27, 1998; Serial No. 60/094,306, filed July 27, 1998; Serial No. 60/100,817, filed September 18, 1998; and Serial No. 60/100,951, filed September 18, 1998.

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Cross-References to Additional Materials

This application incorporates by reference in their entirety for all purposes the following patents and patent applications: U.S. Patent No. 6,097,025, issued August 1, 2000; U.S. Patent No. 5,355,215, issued October 11, 1994; U.S. Patent Application Serial No. 08/840,553, filed April 14, 1997; U.S. Patent Application Serial No. 09/156,318, filed September 18, 1998; U.S. Patent Application Serial No. 09/349,733, filed July 8, 1999; U.S. Patent Application Serial No. 09/337,623, filed August 16, 1999; U.S. Patent Application Serial No. 09/478,819, filed January 5, 2000; and U.S. Patent Application Serial No. 09/643,221, filed August 18, 2000.

This application also incorporates by reference the following PCT Patent Applications: Serial No. PCT/US99/16453, filed July 21, 1999, published as WO 00/05336 on February 3, 2000 (included herewith as Appendix A); Serial

No. PCT/US00/12277, published as WO 00/66269, on November 9, 2000 (included herewith as Appendix B), filed May 3, 2000; and Serial No. PCT/US00/18547, filed July 7, 2000, published as WO 01/04608 on January 18, 2001 (included herewith as Appendix C).

This application also incorporates by reference the following publications: Joseph R. Lakowicz, Principles of Fluorescence Spectroscopy (2nd ed. 1999); and Bob Sinclair, Everything's Great When It Sits on a Chip: A Bright Future for DNA Arrays, 13 THE SCIENTIST, May 24, 1999, at 18.

Please replace the paragraph on page 2, line 15, to page 3, line 2, with the following amended paragraph:

The cost of bioanalytical measurements is roughly proportional to the amount of reagent consumed and to the time spent preparing the reagents, performing the measurements, and analyzing the data. To reduce cost in these measurements, researchers are adopting homogeneous assays and miniaturizing assay volumes. Homogeneous (i.e., "mix and measure") assays generally do not involve filtration steps, which add to the complexity and cost of the measurements. Miniaturizing assay volumes (i.e., miniaturization) generally involves a decrease in assay volume (typically from about 100-200 μL to about 1-10 μL) and/or an increase in microplate well density (typically from 96-well formats to 384, 864, 1536, 3456, or denser formats).

Please replace the paragraph on page 10, lines 11-20 with the following amended paragraph:

Q3

Absorption generally comprises the absorption of electromagnetic radiation by one or more components of a composition. Figure 2 shows a schematic view of a typical absorption experiment, in which incident light is directed from a light source through a composition (and an associated holder), and transmitted light is measured using a detector. Absorption also can be measured using other optical arrangements, such as "epi-absorption," as described in PCT Patent Application Serial No. PCT/US99/16621, filed July 23, 1999, published as WO 00/06991 on February 10, 2000 (included herewith as Appendix D), which is incorporated herein by reference. The amount of light absorbed in passing through a composition can be used to determine the identity, concentration, and electronic energy levels of components of the composition, among other properties.

Please replace the paragraph on page 22, lines 14-20 with the following amended paragraph:

Optical system 90 includes (a) a photoluminescence optical system, and (b) a chemiluminescence optical system, as described below. Further aspects of the optical system are described in the following patent applications, which are incorporated herein by reference: U.S. Patent Application Serial No. 09/160,533, filed September 24, 1998; U.S. Patent Application Serial No. 09/349,733, filed July 8, 1999; PCT Patent Application Serial No. PCT/US99/16287, filed July 26, 1999, published as WO 00/06990 on February 10, 2000 (included herewith as Appendix E); and PCT Patent Application Serial No. PCT/US00/04543, filed February 22, 2000, published as WO 00/50877 on August 31, 2000 (included herewith as Appendix F).

Please replace the paragraph on page 24, line 7 through page 25, line 2 with the following amended paragraph:

A5

Time-modulated source 102 provides light for time-resolved absorbance and/or photoluminescence assay modes, such as photoluminescence lifetime and time-resolved photoluminescence polarization assays. The time-modulated light source may include flash lamps, pulsed lasers, electronically modulated lasers and LEDs, and continuous lamps and other sources whose intensity can be modulated extrinsically using a Pockels cell, Kerr cell, or other mechanism. An exemplary time-modulated source includes a xenon flash lamp, such as a Model FX-1160 xenon flash lamp from EG&G Electro-Optics, as described in U.S. Patent Application Serial No. 09/349,733, filed July 8, 1999, which is incorporated herein by reference. Another exemplary time-modulated source includes a pulsed YAG laser in combination with an optical parametric oscillator (OPO), as described in U.S. Provisional Patent Application Serial No. 60/244,012, filed October 27, 2000, which is incorporated herein by reference. The exemplary sources produce a "flash" or "pulse" of light for a brief interval before signal detection and are especially well suited for time-domain measurements. Extrinsically modulated continuous light sources are especially well suited for frequency-domain measurements. An exemplary external modulator includes an amplitude modulator such as a chopper, as described in PCT Patent Application Serial No. PCT/US99/16287, filed July 26, 1999, published as WO 00/06990 on February 10, 2000 (included herewith as Appendix E), which is incorporated herein by reference.

Please replace the paragraph on page 29, lines 3-15 with the following amended paragraph:

The beamsplitter more generally comprises any optical device for dividing a beam of light into two or more separate beams. A simple beamsplitter (such as a 50:50 beamsplitter) may include a very thin sheet of glass inserted in the beam at an angle, so that a portion of the beam is transmitted in a first direction and a portion of the beam is reflected in a different second direction. A more sophisticated beamsplitter (such as a dichroic or multi-dichroic beamsplitter) may include other prismatic materials, such as fused silica or quartz, and may be coated with a metallic or dielectric layer having the desired transmission and reflection properties, including dichroic and multi-dichroic transmission and reflection properties. In some beamsplitters, two right-angle prisms are cemented together at their hypotenuse faces, and a suitable coating is included on one of the cemented faces. Further aspects of the beamsplitter are described in PCT Patent Application Serial No. PCT/US00/06841, filed March 15, 2000, published as WO 00/55372 on September 21, 2000 (included herewith as Appendix G), which is incorporated herein by reference.

Please replace the paragraph on page 30, line 9 through page 31, line 9 with the following amended paragraph:

The sample holder 124 generally comprises any mechanism for supporting a composition, and particularly a plurality of compositions, for analysis. Suitable sample holders include microplates, PCR plates, biochips, hybridization chambers,

chromatography plates, microscope slides, and gel slabs, among others. These sample holders may include discrete sample sites 126, where distinct samples are separated using any suitable separation mechanism, including walls (microplates and PCR plates), adhesion (biochips), and/or diffusive barriers (gel slabs), among others. These sample holders also may include continuous sample sites, where "samples" are created by separately analyzing different regions of the sample holder. Preferred microplates are described in the following U.S. Patent Applications, which are incorporated herein by reference: Serial No. 08/840,553, filed April 14, 1997; Serial No. 09/156,318, filed September 18, 1998; and Serial No. 09/478,819, filed January 5, 2000. These microplates may include 96, 384, 1536, or other numbers of wells. These microplates also may include wells having elevated bottoms, small ($\leq$ 50 μL) volumes, and/or frustoconical shapes capable of matching a sensed volume. A "standard" microplate includes 96 cylindrical sample wells disposed in a 8 × 12 rectangular array on 9 millimeter centers. Preferred PCR plates may include the same (or a similar) footprint, well spacing, and well shape as the preferred microplates, while possessing stiffness adequate for automated handling and thermal stability adequate for PCR. Preferred biochips are described in Bob Sinclair, Everything's Great When It Sits on a Chip: A Bright Future for DNA Arrays, 13 THE SCIENTIST, May 24, 1999, at 18. Preferred hybridization chambers are described in PCT Patent Application Serial No. PCT/US99/16453, filed July 21, 1999, published as WO 00/05336 on February 3, 2000 (included herewith as Appendix A), which is incorporated herein by reference.

Please replace the paragraph on page 31, line 17 through page 32, line 8 with the following amended paragraph:

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The position of the sensed volume can be moved precisely within the composition to optimize the signal-to-noise and signal-to-background ratios. For example, the sensed volume may be moved away from walls in the sample holder to optimize signal-to-noise and signal-to-background ratios, reducing spurious signals that might arise from luminophores bound to the walls and thereby immobilized. In optical system 90, position in the X,Y-plane perpendicular to the optical path is controlled by moving the stage supporting the composition, whereas position along the Z-axis parallel to the optical path is controlled by moving the optics heads using a Z-axis adjustment mechanism 130, as shown in Figures 5 and 6. However, any mechanism for bringing the sensed volume into register or alignment with the appropriate portion of the composition also may be employed. For example, the optics head also may be scanned in the X,Y-plane, as described in the following patent applications, which are incorporated herein by reference: U.S. Provisional Patent Application Serial No. 60/142,721, filed July 7, 1999; and PCT Patent Application Serial No. US00/18547, filed July 7, 2000, published as WO 01/04608 on January 18, 2001 (included herewith as Appendix C).

Please replace the paragraph on page 32, line 9 through page 33, line 2 with the following amended paragraph:

The combination of top and bottom optics permits assays to combine: (1) top illumination and top detection, or (2) top illumination and bottom detection, or (3) bottom illumination and top detection, or (4) bottom illumination and bottom detection. Same-side illumination and detection, (1) and (4), is referred to as "epi" and may be used for luminescence, epi-absorption, and/or scattering assays, among others. Opposite-side illumination and detection, (2) and (3), is referred to as "trans" and may be used for trans-absorption assays, among others. In optical system 90, epi modes are supported, so the excitation and emission light travel the same path in the optics head, albeit in opposite or anti-parallel directions. However, trans modes also can be used with additional sensors, as described below. In optical system 90, top and bottom optics heads move together and share a common focal plane. However, in other embodiments, top and bottom optics heads may move independently, so that each can focus independently on the same or different sample planes. Further aspects of top and bottom optics are described in the following patents and patent applications, which are incorporated herein by reference: U.S. Patent No. 6,097,025, issued August 1, 2000; and PCT Patent Application Serial No. PCT/US99/16621, filed July 23, 1999, published as WO 00/06991 on February 10, 2000 (included herewith as Appendix D).

Please replace the paragraph on page 36, lines 8-16 with the following amended paragraph:

Q10

More generally, detectors comprise any mechanism capable of converting energy from detected light into signals that may be processed by the apparatus, and by the processor in particular. Suitable detectors include photomultiplier tubes, photodiodes, avalanche photodiodes, charge-coupled devices (CCDs), and intensified CCDs, among others. Depending on the detector, light source, and assay mode, such detectors may be used in a variety of detection modes. These detection modes include (1) discrete (e.g., photon-counting) modes, (2) analog (e.g., current-integration) modes, and/or (3) imaging modes, among others, as described in PCT Patent Application Serial No. PCT/US99/03678, published as WO 99/42817 on August 26, 1999 (included herewith as Appendix H).

On page 42, line 11, please insert Appendices A-H, which are included on the enclosed compact disk.